OBSERVATIONS ON HYPERTENSIVE TOXAEMIA OF LATE PREGNANCY WITH SPECIAL REFERENCE TO EYEGROUND CHANGES THEREIN

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A Thesis

submitted for the Degree of M.D.

in the University of Edinburgh

- 1939 -

INTRODUCTION

The term "Toxaemia of Pregnancy" in its broadest sense includes a number of diverse conditions with no feature in common but that they occur in the gravid state. Hyperemesis gravidarum, acute yellow atrophy of the liver, chorea gravidarum, essential hypertension, chronic nephritis, pre-eclampsia, and eclampsia are all loosely grouped together under this accommodating heading regardless of the fact that some are not toxaemias at all, some may be concurrent with pregnancy and not consequent upon it, and some are neither toxaemic states nor are they exclusively associated with pregnancy.

This paper only concerns the hypertensive toxaemias of late pregnancy - that is to say, cases which in the last trimester show a pathological degree of hypertension. Such a standard is inevitably an arbitrary one, but this is unavoidable. It does not exclude cases of essential hypertension and chronic nephritis because their absolute exclusion has been found impossible, but obvious and gross cases antedating the pregnancy have been omitted from the series.

The remaining cases, practically all of whom apparently developed hypertension as a direct result of their pregnancy, have not been classified in any way. It would appear that until the notorious number of theories concerning late pregnancy toxaemia are finally discarded, and until one is proven and accepted, attempts at classification are unscientific and as fruitless as were the vain efforts of many workers to isolate a specific toxin responsible for the condition.

These theories are so numerous, and the literature concerning them so overwhelming and contradictory that a complete survey is impossible. A summary, however, of the principal facts on which the various theories are based may be attempted.

THE AETIOLOGY OF PREGNANCY TOXAEMIA

A. Mechanical Considerations:

A purely mechanical theory purporting to explain all the typical pathological lesions of eclampsia was put forward by Paramore[1] in 1932. This was by no means entirely original, for last century Lever had expressed the opinion that pressure from the gravid uterus on the renal veins was the cause of albuminuria in toxaemia - it is quite possible that this may have some bearing on the aetiology, for it is impossible to doubt that visceral function is very considerably modified by the great increase in intra-abdominal pressure in late pregnancy. Paramore pointed out that when this pressure is exceptionally high, then the incidence of eclampsia and toxaemia is also high - that is to say, in muscular primigravidae, concealed accidental haemorrhage, hydramnios, and twin pregnancies.

The pressure exerted is primarily on whole organs and then on their capillaries causing stasis. Concentrating on the liver lesions Paramore explained that the typical patchy, irregularly distributed necrosis with haemorrhage was due to short-circuiting of certain sinusoids taking a circuitous route to the central vein of the lobule. These sinusoids would dilate, and ischaemia and necrosis of the adjacent

cells would result. By thus diminishing the capillary bed of the liver, metabolism would be very likely incomplete and detoxication inefficient; toxic products would enter the general circulation, and the condition would be analogous to a partial Eck's fistula. Animals with the liver experimentally short-circuited have convulsions if fed on protein. Popular treatment of pregnancy toxaemia is effective, Paramore thinks, because it modifies the condition of the portal blood by eliminating protein as much as possible.

An experimental approach to the subject along these lines was attempted by Theobald.(2) He injected saline intraperitoneally in dogs and further raised the intra-abdominal pressure by applying a tight abdominal binder at varying intervals to simulate eclamptic fits. Most of these dogs were anaesthetized with chloroform, and when the experiments were repeated by Strauss,(3) he found that the lesions described by Theobald only occurred in dogs anaesthetized with chloroform and not with ether. In any case, the liver lesions were not typical of eclampsia, being usually central and very extensive in some cases with disintegration of the structures in Glisson's capsule. Furthermore, it appears that although the liver lesions in eclampsia, and presumably in pre-eclamptic states, are characteristic,

they are not invariably present, and similar lesions may occur in other conditions such as pneumonia and peritonitis.

One must conclude that this experimental work does not support the mechanical theory of the causation of eclampsia and toxaemia though it by no means proves that raised intra-abdominal pressure has no bearing on the disease. But even if it has, the remaining problem is still identical with the one biochemical workers have been trying to solve from their point of view.

What are the toxic products which gain access to the circulation? Are they substances normally produced which a healthy liver deals with, but which the damaged liver cannot tackle? Or, are they abnormal substances, completely foreign to the healthy organism?

B. Biochemistry of Pregnancy Toxaemia:

Several workers have attempted to explain certain features of hypertensive toxaemia of pregnancy biochemically - for example, as mentioned above, products of incomplete or faulty protein metabolism are supposed to be pressor agents; a raised blood cholesterol with deposition in the intima of smaller vessels eventually causing occlusion and infarction has been considered by some as a possible mechanism

in the pathogenesis of toxaemia; or again, other more recent work seems to indicate that an alteration in certain vital ratios more than in absolute values is characteristic of the condition, and has no doubt some significance, which however is more likely to be secondary than primary.

None of these suggestions offer a theory which is in any way complete, but certain important facts have been elicited which will be listed here in sequence, for the sake of clarity.

1. Concerning the metabolism of nitrogenous substances: Most writers appear to agree that in pregnancy toxaemia and in eclampsia, blood urea and non-protein nitrogen values are normal or low, though there may be some rise late in eclampsia (Stander[4]). This rather suggests that kidney damage is not a primary aetiological factor. Urea nitrogen is diminished in conditions with impaired liver function, and the fact that blood urea is inclined to become lower towards the end of normal pregnancy (Botella Llusia[5]) and still lower in toxaemia, points to the latter organ as being under some strain. The ratio Ammonia : Urea which was stated by Neucki and Pavlov[6] to be an index of liver function, is increased in pregnancy toxaemia (Cullis and Hewer[7]).

In an attempt to assess liver function in pregnancy toxaemia, Cantarow[8] estimated serum bilirubin

in 34 mild cases - he found no increase above the limit of normality given as 1.0 mg. per 100 c.cm. and there appeared to be no relationship between this value and the degree of toxaemia. He also used the Bromsulphthalein test giving 2 mg. per kilo body weight - any retention after 30 minutes is said to indicate liver damage, but the extent of the retention in these cases of toxaemia corresponded neither to the degree of toxaemia nor to the values of serum bilirubin. These results are very inconclusive, but the cases investigated were all mild, and liver function is notoriously difficult to estimate on account of that organ's tremendous reserve. Minor degrees of liver inefficiency are almost impossible to demonstrate.

Uric acid values are definitely increased in toxaemia, as they are in essential hypertension, and they may rise to as much as 8.0 mg. per 100 c.cm. in eclampsia, the upper limit of normality being about 3.0 mg. per 100 c.cm. Uric acid in the body is mostly produced by the oxidation of exogenous purines and up to 70 per cent of this is normally destroyed by the liver (Stander[4]); the remainder is excreted, and can be quite normally excreted, by some badly damaged kidneys. This suggests that the increase in blood uric acid is the result of metabolic disturbance probably originating in the liver. Furthermore, it is known that excretion of uric acid

is depressed by ketogenic diet or any other state in which the alkali reserve is diminished. Anderson[9] found that pre-eclamptics had increased circulating acetone and diacetic acid, and that even in normal pregnancy beta-oxybutyric acid was high. Stander[4] states that lactic acid is increased in eclampsia which is only natural, and suggests using the CO_2 combining power as an index to progress. Certainly, it is an undoubted fact that the CO_2 combining power is usually below normal in pregnancy toxaemia.

Oxidation products such as glutathione and thionine appear to remain within normal limits in toxaemia according to Stander, though they have been the subjects of indictment by other writers.

Guanidine, which is a powerful pressor agent and is said to be increased in the blood in essential hypertension (Major[11]), has also been estimated in pregnancy toxaemia by several workers. Stander found it to be normal, whereas Andes[10] found it raised. It is a substance normally produced in the course of protein metabolism and characteristically increased in arsphenamine poisoning and Laennec's cirrhosis, though not in ordinary cirrhosis, hepatitis or haemolytic jaundice. Intoxication by guanidine causes central necrosis of the liver lobule. In Andes' observations, he found that the increase in blood guanidine followed a rise in blood pressure as a rule,

but bore no constant relationship to it - he also found a decrease to normal values coincident with clinical improvement. He concluded that the increase in this substance is due to the metabolic disturbance in toxaemia, and not the cause of it.

Guanidine, as has already been mentioned, is also increased in essential hypertention and, it seems, in certain epileptiform states. In common with other nitrogenous substances it is high in the puerperium.

2. Lipoids in Toxaemia: Boyd (12) studied lipoid metabolism in pregnancy toxaemia, and found that lipaemia in these states was usually slightly more than in normal pregnancy, though not constantly. Blood cholesterol remained within normal limits, but he found a characteristic increase in the phospholipid : cholesterol ratio in severe and convulsive cases which definitely did not occur in the milder ones. This led him to conclude that the mild cases were not examples of the same condition as the severe ones which he took to be literally pre-eclamptic and comparatively infrequent. The calculations involved in making these estimations appear to be highly mathematical and complicated, but it is stated by Boyd that this ratio does not as a rule alter appreciably in the individual, even during lactation because the fat lost is neutral and does not

affect the ratio which is phospho-lipid : cholesterol (excluding cholesterol ester). He also discovered that the variations occur only in the plasma, and therefore analysis of whole blood for the purpose of estimating this ratio is valueless. The figures given by Boyd for the ratio are:

1.22 average in normal pregnancy

1.61 average in eclampsia

1.40 average in severe toxaemia or "pre-eclampsia"

1.08 average in mild toxaemia

A high ratio is also said to occur in epileptiform states at the time of convulsions.

Phosphorus is hydrophilic, and it is suggested that its increase in the blood and tissues might play some part in the mechanism by which oedema, gross or occult, is brought about in pregnancy toxaemia.

3. Water Balance in Toxaemia: Recently Strauss[13] has written: "In the absence of severe anaemia, venous congestion, acute nephritis, or marked vitamin B deficiency, water retention depends on the plasma protein level and may be influenced by the intake of electrolytes, the chief of which is sodium." He has apparently made a very detailed study of oedema and water balance in connection with toxaemia of pregnancy, and has come to important and interesting conclusions concerning the treatment of these cases.

The three factors controlling the production of

oedema are:

1. Intracapillary pressure
2. Capillary permeability
3. The osmotic pressure of the plasma proteins

Venous pressure from its normal level of 6 to 7 cm. water may increase to as much as 30 cm. in late pregnancy, and filtration from the capillaries is at any rate to some extent proportionate to this, as a high capillary pressure inevitably follows a high venous pressure.

Capillary permeability is increased in certain toxic states, in Vitamin B deficiency, anoxaemia, and disturbed phosphorus : calcium ratio. When oedema is due to increased permeability of the capillaries, the oedema fluid will have a high protein content - as, for example, in acute nephritis - the oedema fluid in toxaemia of pregnancy, however, has a low protein content, and therefore is not due to capillary damage.

Plasma protein levels may be subnormal when the protein intake is deficient, when absorption is defective or when synthesis is inefficient. Loss of albumin via the kidney also depletes the plasma of its protein, and in pregnancy, particularly toxaemic pregnancy, there is, in addition to the possible combination of all these factors, the certainty of the foetal demands. So that in normal pregnancy,

the plasma protein level is low, and in toxaemia it falls still lower, with the albumin fraction reduced more than the globulin. The conventional low protein diet imposed in these cases undoubtedly must exaggerate this phenomenon.

Strauss reports some interesting experiments in this connection. Fifteen ambulant cases of pregnancy toxaemia were given a high protein diet (200 gm. daily) and five controls were given the usual low protein diet (20 gm. daily). At the end of a fortnight, all of the fifteen on high protein diet had steadily lost weight and three had lost gross oedema, the blood pressure fell and albuminuria did not increase; the average non-protein nitrogen increased from 18 mg. per 100 c.cm. to 27 mg. per 100 c.cm., and the foetal mortality was nil. In the five controls, the results were very variable, three improved and two got worse; the plasma osmotic pressure fell by an average of 9% mainly by loss of albumin, whereas in the fifteen cases on high protein diet, there was an average rise of 7%, albumin and globulin fractions increasing equally. The caloric values of the two different diets were for practical purposes identical, and the patients had all had normal blood pressure and urine in early pregnancy. Vitamin B was given daily to the patients in this series, but Strauss[13] later repeated the experiments with controls on ordinary

diets and Vitamin B, showing that Vitamin B was not the cause of clinical improvement.

A further series of experiments by the same worker has shown that the exhibition of sodium salts to toxaemic patients aggravates their disease while ammonium salts improve it. On a uniform low sodium diet of skimmed milk, patients suffering from pregnancy toxaemia lost more weight than could be accounted for by their low calorie intake, and more than was lost by patients on the same diet with chronic vascular or renal disease.

In most cases of toxaemia, Strauss claims a rapid clinical improvement in the withdrawal of sodium, the administration of acidifying diuretics such as ammonium chloride, and a high protein diet. The only cases, he says, which do not respond to this treatment are ones in which the plasma protein level has fallen exceptionally low.

These considerations seem to be more in the realm of physical than organic chemistry, but they are of extreme importance, suggesting as they do a new therapeutic approach to the subject.

4. Other Physical Considerations: In normal pregnancy at term, plasma volume is about + 25% of normal and whole blood volume about + 23%. Haemoglobin, serum protein, and cell volume are also really increased though apparently decreased, as their in-

crease is not so marked as that of the plasma volume. Reduction of these values without haemorrhage means increase in blood volume, or dilution.

Dieckman[14] states that in eclampsia, marked changes in these values may occur with great suddenness. He studied 97 cases of eclampsia and found that during convulsions, haemoglobin, cell volume, and serum protein showed a marked increase and then a slow fall - in other words, that during a convulsion there is concentration of the blood, and clinical improvement is associated with dilution. Failure to dilute was interpreted as a bad sign, and was found sometimes to be associated with hyperpyrexia, increased lactic acid and nitrogen retention, which are all direct results of a small blood volume; heart failure is obviously more likely to occur with increased viscosity of the blood.

In toxaemia of pregnancy, Dieckman found that the changes in blood concentration were similar to those in eclampsia, and he suggested that the common symptoms of headache, visual disturbances, gastro-intestinal upsets, and oliguria might all be referable to concentration, and that they would improve with blood dilution.

The changes in haemoglobin and serum protein bear no direct relationship to each other, but are invariably in the same direction. These changes are not observed in chronic vascular or renal disease

complicated by pregnancy.

The factors controlling blood volume are not definitely known, but removal of the suprarenals, thyroidectomy, and oophorectomy are followed by a fall in blood volume, and hence it is reasonable to suspect an endocrine control. In any case, it seems that although blood concentration is definitely associated with toxaemia of pregnancy and eclampsia, it is not an aetiological factor in their pathogenesis.

After this review of the present state of knowledge regarding the biochemistry of hypertensive toxaemia of pregnancy, one is forced to conclude that, although many workers have attacked the problem of its aetiology from this point of view, its ultimate pathogenesis remains obscure. Many interesting and important facts, however, have been noted and confirmed, but in each case one is left to consider what mechanism initiated the biochemical changes observed, and in what organ the primary lesion occurs. In recent years, endocrinologists have attempted to answer all the questions pondered by physiologists and pathologists since their sciences were defined, and pregnancy toxaemia has received its share of these workers' attention.

C. The Endocrines in Relation to Pregnancy Toxaemia:

An attempt has recently been made by Shute[15]

to classify hypertensive toxaemia of late pregnancy into two diverse types on an endocrine basis. 90%, he says, are not literally pre-eclamptic. They have a persistently high level of circulating oestrogenic substance, and if not treated, very frequently have premature separation of the placenta. Treatment, he says, consists of giving wheat germ oil which is rich in Vitamin E, as for threatened abortion in the early months, and very few cases fail to respond. Vitamin E apparently has the property of antagonizing oestrin.

The remaining 10% of cases, Shute regards as literally pre-eclamptic. They excrete large quantities of Prolan B, the luteinising hormone of the anterior pituitary, and oestrogenic preparations are suggested as useful therapeutic agents in this type. Caution, however, must be exercised to avoid overcompensating and causing abruptio placentae.

The relationship of Vitamin E to progesterone is unknown except that they appear to act in harmony. Treatment of pregnancy toxaemia with progesterone has been attempted by several workers. Robson[67] found that eleven out of twelve cases reacted favourably, and that one which did not react was taken to be literally pre-eclamptic. Marsden[17] treated six cases all of whom had hypertension and oedema, but the results were inconclusive.

Robson and Paterson[16] proved experimentally

that the luteal hormone is manufactured or stored by the placenta as well as by the corpus luteum itself, by removing the ovaries of pregnant rabbits without interrupting the pregnancy. The same workers also showed that while removal of the pituitary gland during pregnancy causes expulsion of the foetus, the pregnancy can be maintained by exhibition of the gonadotropic hormone or prolan A.

Although toxaemia of pregnancy has usually been considered as confined to the human species (the pregnancy disease of Ewes which was described in New Zealand and South Africa about eight years ago, was apparently a nutritional defect and has been practically prevented by the administration of calcium phosphate). Greene[18] has recently described an epidemic condition in rabbits which may have some relationship to eclampsia and toxaemia. The disease had a high incidence in a certain strain of rabbits transmitting a dwarfing hypophyseal defect; it occurred more frequently in the winter months as does eclampsia, and it increased in frequency towards the end of pregnancy, and occasionally occurred post-partum. The condition also occurred in rabbits in a state of pseudo-pregnancy thereby proving that it does not depend for its origin on the products of conception. The pituitary of all rabbits examined during the epidemic period was enlarged, and in cases which developed the disease there was proliferation

of cells in the pars intermedia and evidences of irregular secretion in the anterior lobe. The thyroid was small, and it is of interest to note that Shute maintains the type of true pre-eclamptic toxaemia with excess of circulating prolan B is hypothyroid.

The Smiths and John[19], working out prolan B and oestrin curves for normal and toxaemic pregnancy found high prolan and low oestrin values were characteristic of toxaemia, but they make no mention of different types. They also report that in diabetics who are notoriously susceptible to pregnancy toxaemia, the prolan and oestrin curves tend towards the toxaemic type. These workers suggest that physiological separation of the placenta is a similar process to normal menstruation involving capillary thrombosis, oedema and necrosis. These processes are undoubtedly brought about in menstruation by endocrine action, and as the processes in various organs in toxaemia and eclampsia are very similar in nature it is conceivable that they may be literally "vicarious menstruation" initiated by pathological or at any rate untimely endocrine function.

Progesterone, the luteal hormone, inhibits menstruation, and therefore is suggested in the treatment of toxaemia. Certain results of such treatment have been already mentioned above, but it is difficult to rationalize such treatment where the oestrin content of the blood is low, for in that case one would expect

progesterone to aggravate the condition. Shute recommends oestrin for such cases, and it is impossible to see how two antipathetic hormones can both have a beneficial effect in the same condition.

Smith and Kennard[20] estimated oestrin and progestin in the placentas of normal and toxaemic women within forty-eight hours of delivery. The average oestrin figures were low in toxaemic cases, but low progestin values were not apparently associated either with toxaemia or with spontaneous delivery, though the possibility of a relative deficiency was not excluded.

Also approaching pregnancy toxaemia from an endocrinological point of view is the theory originally put forward by Hofbauer[21] in 1918 suggesting that over-secretion or over-action of the posterior hypophyseal lobe is responaible for hypertensive toxaemia. This was taken up by Anselmino and Hoffman[22] in 1931 who claimed to find a substance in the blood of toxaemic patients capable of reproducing in experimental animals the actions of posterior pituitary extract. This has never been satisfactorily confirmed though Levitt[23] found transient anti-diuresis in rabbits after injection of protein free filtrate of eclamptic serum, similar to that produced by subminimal doses of pitressin. The diuretic rather than the pressor response was used as it is a more sensitive test, and

also it is easier to demonstrate. Cases of toxaemia, chronic nephritis and hypertension all gave normal diuretic curves, whereas filtrates of the serum of dogs given sufficient pitressin to produce a concentration equivalent to about .00002 unit were capable of producing definite inhibition of the diuretic response.

Hurwitz[24] failed entirely to demonstrate any evidence of posterior pituitary hormone in eclamptic serum.

Recently Melville[25] confirmed Marx and Schneider[26] by demonstrating an anti-diuretic substance in normal male and female serum by means of bladder fistula dogs. This substance could not be demonstrated in the serum of normal pregnant women but was present in small quantities in toxaemic pregnancy. Shortly after, Schockaert and Lambillon[27] tried using intravenous vasopressin as a diagnostic test for toxaemia; 3 units Tonéphine in normal pregnancy was followed by a rise in blood-pressure of about 25 mm. Hg. but there were no subjective symptoms, whereas a similar injection in non-pregnant subjects and in pregnancy toxaemia caused as much as 80 mm. Hg. rise in blood-pressure with severe subjective symptoms such as cyanosis, malaise, vomiting, tenesmus and sometimes syncope. Similar results have been obtained by Dieckman and Michel[28] and by De Valera and Kellar[29]. Cases of chronic nephritis react as normal pregnancies.

To form any opinion as to the likelihood of posterior pituitary action being a cause of pregnancy toxaemia, one must attempt to compare the pathological lesions found in eclampsia and toxaemia with those occurring as a result of excessive posterior pituitary in the circulation.

Byrom[30], using rats, did a series of experiments injecting doses of pitressin at various intervals, and killing the animals after varying subsequent intervals. Twenty-four hours after a dose of 30 units, he found wedge-shaped infarcts in the kidneys with coagulative necrosis of the tubules, and in some cases dilatation of the capillaries in the glomerular tuft with swelling and haemorrhage. If the animal were killed months after the dose of pitressin, the kidney was found to be deformed by cortical scars but the tissue in between was normal. As no thrombi were seen, the infarcts were assumed to be the result of spasm. If smaller repeated doses of pitressin were given, necrosis of isolated groups of cells was found in the renal cortex with degeneration of the tubules but no glomerular lesions. In the vessels themselves, lesions were found in the media and were in the nature of focal necrosis in bigger vessels and lysis in smaller ones. These lesions are similar to those found near the site of injection of adrenalin, and therefore, are probably due to spasm.

The liver lesions produced by the injection of pitressin were mostly periportal, but not consistently - the cells were swollen at first and later shrivelled with disappearance of the nuclei.

Necrotic patches were observed in the gastric mucosa corresponding to underlying vascular lesions.

All these lesions have points of similarity with typical eclamptic lesions, though they are not entirely analogous. The smaller the doses of pitressin, and the larger the period over which they are given, the more do the resultant lesions resemble those of eclampsia, and the kidney lesions which follow the larger doses bear a singular resemblance to the condition known as bilateral cortical necrosis of the kidney. The pathology of both these conditions will be discussed presently, but it must be noted here that the quantity of pitressin which would have to be circulating to produce such lesions could not conceivably be present in the circulating blood; therefore some other agent must be at least partially responsible for their pathogenesis, or alternatively the vessels may be in a hypersensitive state, or thirdly, the hormone might be fixed in some way by the tissues and vessels.

D. Pathology of Pregnancy Toxaemia.

The typical hepatic lesions of eclampsia have already been described, and it is apparent that if

toxaemia is literally pre-eclamptic, the liver must show similar if milder changes. They consist of patchy areas of necrosis usually somewhere near a branch of the portal vein but not characteristically occupying any particular zone of the liver lobule. In severe cases this necrosis may be extensive with rupture of dilated sinusoids and haemorrhage. These lesions are adequately repaired if the case is not fatal by the regenerative power of the liver cells.

In the kidney the case is different. The renal units have no powers of regeneration, and the initial acute lesions are followed by permanent ones. The kidneys of a fatal case of eclampsia usually show ischaemic necrosis of the glomeruli with degenerative changes in the tubules (McKelvey and McMahon[31]) (Herrick and Tillman[32]). Post-mortems performed years after eclampsia or toxaemia have frequently demonstrated renal lesions similar to those found in essential hypertension in association with widespread vascular disease, rather than primary renal lesions.

Attention was first drawn to the vascular lesions of eclampsia by Volhard[33] in 1918, who propounded the theory that toxaemia of pregnancy is a process initiated by widespread arterial spasm. He showed that the typical renal lesions are ischaemic and due probably to spasm of the afferent arteriole to the glomerulus, but he did not describe other vessels in

much detail. Irving[34] supported this theory and added that the permeability of the capillaries in the ischaemic glomeruli is increased allowing the passage of albumin which forms casts in the tubules when there is insufficient fluid to prevent it. Hinselmann[35] reported spasm of the arterioles in the nailfold in toxaemia, and Mussey[36] of the Mayo Clinic found the same thing in muscle, with stasis in the capillary loops. In 1927 Jaffé[37] reported changes in the cerebral vessels of a fatal case of eclampsia which he thought started in the media and later involved the intima causing occlusion and ultimately necrosis of the smaller distal branches.

In 1935 McKelvey and McMahon[31] described the renal lesions in cases of toxaemia not immediately fatal - the entire arterial tree showed hypertrophy. In the larger vessels of the kidney, the media showed thickening, and there was connective tissue increase in the intima and adventitia. The smaller vessels showed thickening of the intima with frequent occlusion and haemorrhage in the vessel wall. 90% glomeruli were well preserved, but they were enlarged, proliferative and the capillaries of the tuft were dilated and sometimes ruptured into the capsular space. The tubules were mostly small and atrophic, and some had disappeared altogether. There was a diffuse fibrous tissue increase.

Similar vascular lesions were noted in the pancreas and suprarenals, and the relationship with malignant nephrosclerosis was indicated. The latter condition, first described by Volhard and Fahr in 1914 is characterized by hypertension and uraemic death; small arteries throughout the body show proliferative endarteritis, and focal lesions of the kidney units similar to those described above, occur.

Authorities are not all agreed that arterial spasm is invariably the primary lesion in pregnancy toxaemia. Herrick and Tillman attempt to differentiate a renal type from the vascular type, and report that in eleven post-mortems, four cases showed primary glomerulo-nephritis and the other seven had primary vascular disease. Many clinical workers support this view (Mussey and Keith[38], Peckham[39] and others) but it is possible that those cases classified as primary nephritis, may in reality be examples of vascular disease which attacked the kidney to the comparative exclusion of other tissues.

The relationship of pregnancy toxaemia to the various types of vascular and renal disease associated with hypertension is evidently very intimate, but a common aetiological factor has not yet been discovered.

A condition which may have some bearing on this relationship is bilateral cortical necrosis of the kidney. It is a rare condition and Von Zalka[40] in

1932 was only able to collect 37 cases from the literature. Of these, 31 were associated with pregnancy, three occurred in males and the other three in non-pregnant women. Clinically the condition is characterized by anuria which may be complete, and death occurs from uraemia; in cases associated with pregnancy, fits, similar to eclamptic fits have been observed. Post-mortem, both kidneys are enlarged, and yellow patches of degeneration and haemorrhage appear on the surface. The cut surface shows necrosis of the entire renal cortex which is dry and yellowish - there is haemorrhage in the otherwise normal medulla. The cortex is filled with innumerable small infarcts with haemorrhagic borders which are so numerous that they become confluent. Histologically there are thrombi in the interlobular arteries, afferent arterioles and glomerular capillaries. The only intact glomeruli are those in the boundary layer between cortex and medulla which presumably derive a blood supply from the medulla as well as from the cortex. This condition appears to be of a similar nature to the typical renal lesions of eclampsia described above, but of a very much severer degree. The fact that it undoubtedly occurs apart from pregnancy suggests that possibly toxaemia of pregnancy is not a reaction to some specific substance provoked directly or indirectly by the products of conception, but rather a specific reaction on the part of the

vessels to certain circumstances most frequently in pregnancy but also,possibly apart from the gravid state with dramatic suddenness in bilateral cortical necrosis of the kidney or more chronically in nephrosclerosis and essential hypertension. The two latter conditions are probably due to the same underlying pathological process, its manifestation depending on which group of vessels are chiefly affected and to what degree. The agent or agents causing the vasoconstriction in these conditions is as obscure as its analogue in pregnancy toxaemia, and the question of their relationship is as yet a matter for conjecture only; the recent work on hypertension by Pickering[41] and by Byrom and Wilson[42] however, is interesting in this connection, and will be discussed later.

Certain agents conceivably responsible for the vasoconstriction in pregnancy toxaemia have already been mentioned - notably, posterior pituitary hormone and guanidine or allied nitrogenous substances, but there are others which have been suspect, for example, bacterial toxins from fermentation in the large intestine, chorionic villi which somehow have managed to invade the maternal circulation(Schmorl), intracellular ferments from the placenta (Dryfus) and, a more conceivable theory, toxic autolytic bodies from placental infarcts (James Young[43]). Unfortunately for this interesting suggestion, placental infarcts frequently occur apart

from toxaemia, and toxaemia occurs without placental infarcts; further, it is difficult to explain post-partum cases of eclampsia on this basis. Nevertheless, placental infarcts are undoubtedly very common in toxaemia and eclampsia.

E. Allergy in Relation of Pregnancy Toxaemia.

Many workers for a long time endeavoured to isolate a specific toxin from the serum of eclamptic and toxaemic patients, but none had any success; it is possible, however, that some substance may be responsible for the condition not because of its own inherent qualities but because of hypersensitivity on the part of certain individuals to it. Some facts concerning eclampsia seem to favour this view, the chief among which are that it rarely recurs and is most common in primigravidae; the same, however, does not apply to toxaemia.

Recently Belikoff[44] has reported positive skin reactions in toxaemic patients after the intradermal injection of eclamptic serum - the reactions produced were suggestive but by no means sufficiently constant to constitute a diagnostic test though they were usually negative in normal pregnancy and in cases of essential hypertension and nephritis complicated by pregnancy.

It may be that any or all of the agents mentioned above as possible vasoconstrictors, may in a hypersensitive maternal organism induce vascular spasm. In

other words, it is suggested that arterial spasm is an allergic reaction to various non-specific chemical stimuli which frequently occurs in pregnancy, and initiates the condition known as hypertensive toxaemia of pregnancy.

It is interesting to note in this connection the work of Arnott and Kellar[45] on acute nephritis. This work indicates that the latter condition is in the nature of an allergic reaction to the products of streptococci, rather than a directly defensive one. Acute nephritis, however, is not considered now by most authorities to bear any close relationship to eclampsia and toxaemia, though formerly in view of the clinical similarity, such a connection was considered likely.

THE OPHTHALMOLOGICAL EXAMINATION OF TOXAEMIC PATIENTS

The only practicable way of observing the smaller blood vessels during life is by ophthalmoscopic examination of the ocular fundi. Although a considerable amount has been written on this method of examination of cases of pregnancy toxaemia in Germany and America, it has apparently received scant attention in this country. The only English paper found on the subject is one by Grace Jones[46] in 1937 - she examined the fundi of 144 patients with hypertensive

toxaemia of various grades of severity, and described retinal changes such as oedema and retinitis, but she did not pay much attention to the vessels. Most of the authorities, however, concentrate on the vessels and assert that all other changes in the retina in this condition are secondary to a primary vasoconstriction.

In 1923 Hinselmann[35], after examining the fundi for toxaemic patients for vascular lesions, reported that the choroidal vessels seemed to be more affected than the retinal ones. This is not confirmed in the present paper, but a certain number of cases were observed which showed definite changes in the choroidal circulation. This is particularly interesting in view of the fact that it has been frequently assumed that the retinal vessels are an accurate index to the state of the whole vascular tree - such an assumption is not supported by the present investigation. There appears to be no reason why vessels in different tissues should react to a stimulus in an identical manner and to precisely the same degree, and there is no reason to suppose that the stimulus is equally received in the various tissues. In fact, in this condition of pregnancy toxaemia, and in the allied condition of essential hypertension it seems likely that the stimulating agent causing vasoconstriction is not circulating, but is probably fixed in some way by the vessels or tissues. If vessels as anatomically close to each other as the choroidal and retinal ones do not

invariably share a stimulus, how much more frequently is it probable that the same stimulus is not shared by the retinal and, for example, the hepatic vessels?

In 1929, Mylius[47] took repeated photographs of the fundi of twelve cases of toxaemia and demonstrated spasm of the retinal vessels which he described as "bowl-like dippings" passing over the vessel at varying intervals and lasting for variable periods. In some cases retinal oedema was present, but it was invariably preceded by venous dilatation; in other cases actual exudates and haemorrhages occurred.

Wagener[48] in 1933 described toxic constriction of the retinal arterioles which he said was present in 70% of the cases examined. In 60% of these there was no residual lesion in the fundus after termination of the pregnancy. The constrictions might affect any or all branches of the central artery. If this is so, and it seems to be, then it also suggests that all vessels do not react similarly to the stimulus causing the spasm.

Other writers (Gibson[49], C.S.Fan[50]) say that although spasm of the retinal arterioles does occur, general attenuation without localized constriction is more frequently observed in the fundi of patients with hypertensive toxaemia. Masters[51] actually measured the retinal vessels and claimed to find narrowing in every case where the systolic blood-pressure exceeded

150 mm. Hg. Heightening of the arterial reflex which occurs commonly in these cases is taken by some as evidence of attenuation (Gibson[49]), but others appear to think it can occur apart from narrowing of the vessels and is probably due to deposition of cholesterol in the vessel wall. In the present series of cases, heightened arterial reflex was frequently present when there was no obvious narrowing of the vessels, but it is possible that minor degrees of vasoconstriction were not appreciated; as the blood cholesterol was never raised but was usually at a low level, it seems unlikely that its deposition accounted for the heightening of the reflex, and further, the phenomenon would not disappear as rapidly as it sometimes did if it were due to such an organic process.

This investigation was undertaken with the hope that some differentiation of types might emerge, enabling the early detection of potential eclamptic and severe cases from the milder ones. This primary objective was not attained. As an aid to remote prognosis, it may be that the ophthalmoscope is of more value, though this cannot be stated definitely in view of the absence of a satisfactory follow-up period.

Report of Cases

The individual patients in this series of cases were not selected on account of any clinical manifestations or otherwise. The sole criterion was the blood-pressure which at some time exceeded 150 mm. Hg. systolic or 90 mm. Hg. diastolic. No cases of known cardiovascular or renal disease ante-dating the pregnancy were included, though one patient probably had essential hypertension (XII).

With the exception of three patients who were treated as out-patients, all the cases were on the same régime. Protein was restricted but not drastically, and salt was reduced to a minimum; most patients were ambulant unless they showed gross oedema. Weights were recorded twice weekly, but except where gross oedema was lost, no remarkable increases or losses were noted; no cases however developed an acute exacerbation or eclampsia while in hospital, so it is not reasonable to draw conclusions as to the value of weight taking in the present series.

All patients were under observation for at least a fortnight prior to delivery, most of them for much longer. In-patients were examined ophthalmoscopically twice weekly, and out-patients, weekly; if any fundus change was observed they were examined daily. The examination commenced at the time the blood-pressure was first noted to reach the stated figure, and continued to the end of the puerperium. Where possible it was repeated six weeks after delivery.

Routine estimations of blood urea, cholesterol, CO_2

combining power and uric acid were made, and in some cases urea clearance tests, in the hope that some correlation might be found with the fundus lesions.

The cases have not been classified in any way, and will be reported in the order in which they were seen.

Case I. E.T. aet. 45. 13 gravida.

This patient was first seen on November 11th and was due on January 15th. All previous pregnancies were normal as far as she knew and there was no reason to suspect any renal disease. The blood-pressure was 140/85 and the urine was clear. Out-patient treatment did not lower the blood-pressure, and she was admitted on December 12th with blood-pressure 155/90, no albumin, oedema or symptoms. The fundi were normal.

Blood urea	22 mg. per 100 c.cm.
Blood cholesterol	98 mg. per 100 c.cm.
Blood uric acid	3.9 mg. per 100 c.cm.
CO_2 combining power	46.2 vols. per cent.

Urea concentration was good. The blood-pressure remained at the same level and the fundi remained normal till delivery which occurred spontaneously on January 2nd. The infant was healthy.

On January 3rd the blood-pressure was 115/70 and after a slight rise to 130/80 on the third day it subsided to 120/70 and remained at that level till the end of the puerperium. The fundi remained normal.

This case is of interest, as it shows that a

woman after thirteen pregnancies can still have an apparently healthy vascular system. Unfortunately she was not seen early in pregnancy, but the fall in blood-pressure in the puerperium and the normal fundi suggest that the hypertension was due to the pregnancy and not to vascular disease. If this hypertension was due to vasoconstriction then the latter must have been localized to tissues other than the retina, unless the changes in the retinal vessels are so transient that they can be missed even with repeated examinations. In the latter case it would be sheer waste of time to attempt to examine fundi in toxaemic patients, and a negative examination would indicate nothing at all.

Case II. J.P. aet 21. 2 gravida.

This patient's first pregnancy, two years previously had been complicated by mild hypertension but no albuminuria and she had delivered an anencephalic foetus. The blood-pressure had been normal after delivery, and there was no other relevant history. She was not seen again until October 12th 1938 when she was 30 weeks pregnant and her blood-pressure was 154/96. She did not improve, and on November 15th she was admitted.

On admission blood-pressure was 170/120, the patient complained of headache and vomiting, and there were large quantities of albumin in the urine. The

ocular fundi showed no abnormality at this or any other time.

Blood urea	25 mg. per 100 c.cm.
Blood cholesterol	130 mg. per 100 c.cm.
Blood uric acid	4 mg. per 100 c.cm.
CO_2 combining power	42 vols. per cent.

There was no gross oedema, but the patient gained 3 lbs in eight days.

Urea concentration was satisfactory.

With conservative treatment, the symptoms abated but the blood-pressure rose to 185/120 and the albuminuria increased, so labour was induced by rupturing the membranes on November 26th, and a normal premature infant was delivered. After delivery the blood-pressure dropped to 125/70 but subsequently rose gradually to 155/90 at which level it remained, and a trace of albumin remained in the urine. Unfortunately this patient did not report for subsequent examination six weeks after delivery.

This case, when admitted to hospital, was apparently pre-eclamptic, and yet no change was observed in the fundi throughout. In view of the history, and the persistent elevation of the blood-pressure after delivery, it seems probable that some permanent vascular lesion had occurred though months of observation would be necessary to confirm this. It is doubtful if a vascular lesion of the kidney can have been entirely to blame, as renal function was not seriously impaired.

In a severe metabolic disturbance such as this evidently was, the liver must be suspect.

Case III. M.P. Aet.27. Primigravida.

This patient was due on January 1st. She was seen first on July 27th, at this time urine and blood-pressure were normal, and there was no relevant history.

On September 9th, blood-pressure was found to be 165/85 and there was marked albuminuria. She was admitted forthwith, and after a few days rest the blood-pressure fell to 125/70 and the albumin disappeared from the urine.

Blood urea	18 mg. per 100 c.cm.
Blood cholesterol	160 mg. per 100 c.cm.
Blood uric acid	4.2 mg. per 100 c.cm.
CO_2 combining power	44.2 vols. per cent.

At this time the patient lost 4 lbs in a week while in hospital, and then was discharged. Urea concentration was good.

The blood-pressure remained normal till October 28th when it rose again to 160/90, but there was no albuminuria. The fundi were examined at this time and the arteries were definitely narrowed, and the choroidal pattern suggested sclerosis of these vessels. On November 4th the patient was re-admitted to hospital with the urine loaded with albumin and blood-pressure 185/110 - she was vomiting and complaining of epigastric pain. The fundi had not changed from the previous week. No spasm of the arteries was observed. Conservative treatment was

attempted, as the patient appeared to be on the verge of eclampsia, but the blood-pressure rose to 210/110, so labour was induced by rupturing the membranes. A live premature infant was delivered.

The puerperium was uneventful, and the blood-pressure fell to 120/70 at which level it remained. When the patient was discharged, the urine was free of albumin and the retinal vessels were normal, but the choroidal pattern remained as before.

This case suggests an acute process subsiding rapidly - there was nothing to indicate any previous vascular disease except the suggestion of choroidal sclerosis. The constriction of the retinal vessels definitely disappeared with the termination of pregnancy, and the blood-pressure remained normal six weeks after delivery suggesting that there was no permanent vascular lesion though by no means proving it.

Case IV. L.D. Aet.22. Primigravida.

This patient had no relevant history; she was first seen on July 7th, 14 weeks pregnant, with blood-pressure and urine normal.

On November 4th the blood-pressure was 140/85 and five days later she was admitted with blood-pressure 160/90 and moderate albuminuria but no symptoms or oedema. At this time the fundi showed narrowing of all the retinal arteries and there was slight oedema of both discs.

Blood urea	25 mg. per 100 c.cm.
Blood cholesterol	104 mg. per 100 c.cm.
Blood uric acid	3 mg. per 100 c.cm.
CO_2 combining power	51.0 vols. per cent.

Urea concentration was good, and no excessive increase in weight was recorded.

Re-examination of the fundi revealed exposure of choroidal vessels peripherally, but no suggestion of sclerosis; the retinal vessels remained narrow and there was heightening of the arterial reflex. The oedema of the discs remained about the same.

This patient was spontenaously delivered on November 21st; the puerperium was uneventful, and the blood-pressure was 130/85 when she was discharged from hospital; six weeks post-partum it was 130/80.

This case was clinically much less severe than the two preceding ones, but the fundus changes were very much more marked. This may mean that the vessels of the organ responsible for the metabolic disturbances of toxaemia was relatively unaffected, or that the retinal vessels and possibly others were singled out for affection.

The blood-pressure did not subside by the end of the puerperium in this case, and nor did the retinal vessels regain a normal calibre, suggesting that the process was not altogether acute.

Case V. R.C. Aet.32. Primigravida.

No history of any note was obtained in this case, the patient was due on January 8th and was first seen on October 28th with blood-pressure 148/85 and a trace of albumin in the urine. She was treated as an out-patient with some benefit at first, but had to be admitted on December 16th with blood-pressure 160/100 and marked albuminuria but no symptoms. The fundi were normal at this time and no narrowing of the vessels was observed.

Blood urea	18 mg. per 100 c.cm.
Blood cholesterol	110 mg. per 100 c.cm.
Blood uric acid	2.2 mg. per 100 c.cm.
CO_2 combining power	49.4 vols. per cent.

Urea concentration was good.

Repeated examination of the fundi revealed no abnormality, but the clinical condition did not improve and labour was medically induced on December 31st.

After an initial drop, the blood-pressure rose again to 145/90 and was at this level on discharge with a trace of albumin in the urine.

It is possible that early vascular disease was present here and merely dramatized by the pregnancy, but if so, no sign of it was obvious in the retinal vessels. The patient did not report for post-natal examination though particularly advised to do so.

Case VI. S.T. Aet.23. Primipara.

This was a primipara due January 12th. There was no relevant history.

She was first seen in September when the blood-pressure was 126/80 and the urine clear. No signs of toxaemia were noticed until she attended the ante-natal clinic on December 12th with blood-pressure 156/95, marked albuminuria and considerable oedema of the legs, hands and face. She was admitted to hospital the same day.

Blood urea	20 mg. per 100 c.cm.
Blood cholesterol	154 mg. per 100 c.cm.
Blood uric acid	3.6 mg. per 100 c.cm.
CO_2 combining power	48.4 vols. per cent.

Urea concentration was satisfactory. The weight was 12st. 4 lbs.

The fundi were normal.

With rest and low protein diet the weight decreased by 5 lbs in a fortnight, and the urine became clear of albumin. The blood-pressure remained at 150/95 but the patient went home against advice on December 24th.

On January 4th she was re-admitted with albuminuria again and blood-pressure 165/95. The weight was 12st. 3 lbs.

Ophthalmoscopic examination revealed constriction of the retinal arteries which remained until after delivery on January 13th following medical induction.

At the end of the puerperal period the blood-

pressure was still 135/90, but there was no albuminuria and the fundi were normal. The patient did not report post-natally.

Toxaemia in this case was of moderate severity, and the narrowing of the retinal arteries which disappeared after delivery seemed to be in keeping with the hypertension. The latter, however, did not subside altogether after the termination of the pregnancy, therefore one is again forced to conclude that the changes in the entire vascular tree were not entirely uniform, and that somewhere vascular constriction persisted although it relaxed in the retina.

There was no suggestion of vascular disease antedating the pregnancy in this case, and if the hypertension continues to persist, this patient will eventually become a case of chronic vascular disease which definitely dates from a pregnancy.

Case VII. K.P. Aet. 30. Primipara.

This patient was a primipara due on January 21st. She had no history suggesting renal disease, and the blood-pressure when she was first seen in September was 135/85.

No untoward signs were noted in the course of the pregnancy until January 6th when the blood-pressure was found to be 160/90. There was no improvement after a week's out-patient treatment, so she was admitted.

Blood urea	26 mg. per 100 c.cm.
Blood cholesterol	94 mg. per 100 c.cm.
Blood uric acid	2.8 mg. per 100 c.cm.
CO_2 combining power	50.4 vols. per cent.

Urea concentration was normal.

The retinal vessels were normal, but the choroidal pattern suggested sclerosis.

The blood-pressure remained about 153/90 until after the patient spontaneously delivered herself on January 20th.

During the puerperium the blood-pressure subsided to its original level of 130/80 and remained there.

This was clinically a mild case and there is little to note in connection with it apart from the suggestion of choroidal sclerosis and the rather high initial blood-pressure, the two facts suggesting perhaps that the vascular system was not entirely healthy prior to the pregnancy, and that the pregnancy merely exaggerated temporarily a case of early vascular disease.

Case VIII. Aet. 22. H.P. Primigravida.

This patient was a primigravida due on January 22nd. She had no relevant past history, and was first seen at the ante-natal clinic on October 18th. At that time the blood-pressure was 125/80, but the urine showed a trace of albumin. Six weeks later she was admitted with blood-pressure 150/90 and marked

albuminuria. The ocular fundi at this time showed no change from normal.

With in-patient treatment the blood-pressure fell to 130/80, but a trace of albumin persisted in the urine. At her own request she was discharged at this time.

A fortnight later she was re-admitted again with marked albuminuria and blood-pressure 135/85. This time definite spasm of the smaller branches of the retinal artery was noted.

Blood urea	19 mg. per 100 c.cm.
Blood cholesterol	134 mg. per 100 c.cm.
Blood uric acid	3.8 mg. per 100 c.cm.
CO_2 combining power	46.6 vols. per cent.

Weight showed no abnormal increase and there was no oedema. Urea concentration was satisfactory.

For three weeks the pregnancy was allowed to continue in view of the absence of symptoms and the relatively mild nature of the signs. The blood-pressure did not again rise above 135/90, but spasm of the retinal vessels persisted, and just before delivery a small haemorrhage appeared in the right eye.

The membranes were ruptured at term, and a live infant was normally delivered.

The blood-pressure subsequently fell to 100/70 and remained low throughout the puerperium. The spasm of the retinal vessels ceased and the haemorrhage re-absorbed. Six weeks post-partum, the blood-

pressure was still 100/70.

This is a most interesting case which would never have been ophthalmoscopically examined at all but for the fact that one high blood-pressure reading was recorded at the ante-natal clinic.

There can be no doubt that the spasm of the retinal vessels was due to the pregnancy in this case, as it disappeared immediately on the latter's termination. Further, it is obvious that if spasm of the arterioles were going on throughout the body as in the retina, the blood-pressure would have been higher than 135 systolic. Therefore one must conclude that this tonic constriction was localized - it definitely occurred in the retina, and it probably occurred at the same time in the cerebral vessels; the persistent albuminuria suggests that it may also have occurred in the renal arterioles, but the absence of severe metabolic disturbance probably indicates that the liver was comparatively unaffected together with many other tissues.

Case IX. L.B. Aet. 25. Primigravida.

This patient was another primigravida due at the end of January. No relevant history was elicited.

When first seen in October, the blood-pressure and urine were normal.

She was admitted to hospital on December 2nd with a blood-pressure of 175/90 but no albuminuria.

The retinal arteries at this time appeared to be rather narrow but no spasm was observed. On December 20th the patient went home against advice with blood-pressure 150/90 but no other symptoms or signs apart from the narrowing of the retinal arteries.

On December 28th she was re-admitted with blood-pressure 180/100, but no symptoms or albuminuria. The weight had shown only normal increase. At this time the retinal arteries were distinctly narrowed.

Blood urea	22 mg. per 100 c.cm.
Blood cholesterol	77 mg. per 100 c.cm.
Blood uric acid	3.2 mg. per 100 c.cm.
CO_2 combining power	48.2 vols. per cent.

Urea concentration was normal.

The condition remained about the same, and no other alteration was noted in the retinal vessels though the margins of the discs became hazy.

The membranes were ruptured on January 14th and a live infant was delivered.

After an initial drop in the blood-pressure it rose again to 165/90 and when the patient was discharged it was 170/90 and the retinal vessels still showed definite constriction.

This case suggests that permanent vascular disease initiated by the pregnancy has established itself, and it is to be noted that here hypertension was the only sign of any pathological process during the pregnancy. The retinal vessels confirmed the blood-pressure

readings, and it is possible that the vasoconstriction may have been widespread in this case rather than localized. In the absence of any symptoms, however, and with no albuminuria at any time, the visceral circulation cannot have been grossly interfered with.

Again before any definite pronouncement can be made, a prolonged follow-up period is necessary, but the blood-pressure readings and ophthalmoscopic findings are certainly suggestive.

Case X. F.A. Aet.24. Primigravida.

This patient, due on February 2nd, was admitted to hospital with pyelitis on October 8th. Her previous history revealed nothing of note. The blood-pressure at that time was 130/85. The pyelitis cleared up rapidly and she was discharged a fortnight later.

On December 30th, the blood-pressure was found to be 150/90, but there was no albuminuria and no symptoms. At this time the retinal arteries were distinctly narrow with active spasm in some cases, and patches of heightened arterial reflex. The choroidal vessels were unmasked but there was no suggestion of sclerosis.

On January 8th the patient was re-admitted with blood-pressure 150/90 but no albuminuria.

Blood urea	25 mg. per 100 c.cm.
Blood cholesterol	142 mg. per 100 c.cm.
Blood uric acid	3.4 mg. per 100 c.cm.
CO_2 combining power	40.2 vols. per cent.

There was no oedema and no abnormal increase in weight.

Urea concentration was good.

A week later (January 15th) although the blood-pressure had risen to 160/95, no spasm could be seen in the retinal arteries, but three days later it was observed again. Albumin also appeared in the urine. On January 20th the patient was normally delivered. During labour spasm of the retinal arteries was still obvious, but the following day it had disappeared and was not observed again although the blood-pressure remained high and was 145/85 at the end of the puerperium.

A month later this patient was seen again, and by this time the blood-pressure had dropped to 125/80. The retinal arteries were quite normal.

This case emphasises the extremely transitory nature of the fundus changes particularly oedema and spasm. This was observed repeatedly. Again it is to be noted that the fundus picture bears no constant relationship to the blood-pressure (cf. Case VIII).

The fact that the spasm of the retinal arteries disappeared after delivery in spite of persistent elevation of the blood-pressure in the puerperium, may be of some significance as regards remote prognosis. It is well-known that it is impossible to base such a prognosis on the presence or absence of hyper-

tension in the puerperium, but its presence is always suggestive. Here, however, the hypertension had disappeared six weeks post-partum following the disappearance of arterial spasm immediately after delivery. Unfortunately at least a year, perferably many years of observation is necessary to make any deductions of real value from these facts.

The frequency of pyelitis in cases of toxaemia and vice versa has often been remarked. It is suggested that an over-active endocrine substance exaggerates the dilatation of the renal pelvis and uterus which normally occurs in pregnancy. Ureteral drainage has been recommended by certain enthusiasts (Hess[52]) as a therapeutic measure in toxaemia.

Case XI. A.H. Aet.40. 3-gravida.

This was a 3-gravida due on January 13th. Her other two pregnancies had been uneventful, and there was no history suggesting renal disease.

When first seen at the ante-natal clinic on September 7th the blood-pressure was 115/70 and the urine was clear.

On January 10th the blood-pressure was 146/85 and a trace of albumin showed in the urine. She was treated as an out-patient for a fortnight, but, on January 26th blood-pressure was 160/100 and the albuminuria had become more marked, so she was admitted.

At this time the fundi showed narrowing of the arteries and a few white dots but no definite spasm.

Blood urea	24 mg. per 100 c.cm.
Blood cholesterol	164 mg. per 100 c.cm.
Blood uric acid	4 mg. per 100 c.cm.
CO_2 combining power	46.6 vols. per cent.

Urea concentration was satisfactory, and though the woman was obese, there was no oedema or abnormal weight increase.

The condition remained about the same, and the patient was normally delivered on February 4th. After this the blood-pressure slowly fell and was 130/80 when she was discharged. On February 13th, however, when the fundi were examined definite slow spasm of many branches of the retinal artery was seen.

On March 13th this patient was seen again; the blood-pressure was then 135/80, and the retinal arteries were narrow but no spasm was noted.

It is impossible to guage the significance of the facts in this case. Spasm which was more definite and obvious than in any other case in the series was only observed in the puerperium when the blood-pressure had fallen to a comparatively normal level. Being by this time aware of the extremely transitory nature of this phenomenon, the most probably explanation is that when the fundi were examined ante-partum, the times chosen happened to be all unfortunate and that spasm was present in some of the intervals.

This conclusion is very depressing because it means that unless one is prepared to examine a patient ophthalmoscopically every few hours, it is very little use examining them at all, and that the failure to observe any fundus lesion even on repeated examination does not exclude the possibility of its presence in the intervals.

Case XII. E.T. Aet.39. Primigravida.

This patient was a primigravida. She had had one miscarriage two years previously and suffered from mitral stenosis, which appeared to be well compensated. She was due on February 2nd.

When first seen at the ante-natal clinic on October 4th, the blood-pressure was 180/120 and she complained of headache. She was admitted immediately, and the blood-pressure subsequently fell to 150/90 at which level it remained. There were occasional traces of albumin in the urine, but no oedema or any further symptoms. She went home at her own wish on October 14th.

On October 28th she was re-admitted, with blood-pressure again 180/115 and moderate albuminuria.

At this time the fundus showed heightening of the arterial reflex and fullness of the veins. A week later, when the blood-pressure had fallen to 150/90, there was definite crushing of the veins.

No arterial spasm was seen.

The blood urea was 33 mg. per 100 c.cm, which is rather high for a pregnancy value, but both urea concentration and clearance tests were quite satisfactory.

Blood cholesterol	107 mg. per 100 c.cm.
Blood uric acid	4.2 mg. per 100 c.cm.
CO_2 combining power	46.2 vols. per cent.

The blood-pressure remained about 155/100 and the fundus did not alter mich except that the crushing of the veins varied in intensity, until the patient was delivered by classical Caesarean section on January 12th.

On January 13th the blood-pressure was 184/120 and two days later it was 180/110. The fundus was as before and a few white dots appeared near an artery in the left eye. Blood cholesterol was repeated and was only 104 mg. per 100 c.cm, so that it seems unlikely that the white dots were due to deposition of cholesterol.

On January 25th the blood-pressure was 190/120, but the fundus was unchanged except that the white dots had disappeared again.

A week later there was some haziness of the margin of the left disc, but this subsequently disappeared, and the patient was discharged on February 8th with blood-pressure 170/95, urea clearance normal, and the fundus showing heightened arterial reflex but no crushing of veins or other abnormality. On March 15th blood-pressure was 180/100 and fundi unchanged.

There can be little doubt that this was a case of chronic vascular disease ante-dating the pregnancy and dramatized by it. It was included in the series mainly for comparison, and the fundus picture did seem to be of rather a different variety to the others examined.

The most remarkable features in this fundus (the right fundus was obscured by a corneal opacity) were the marked heightening of the arterial reflex and crushing of the veins. Spasm was not noted at all.

Case XIII. E.J. Aet.23. Primigravida.

Due February 5th. This patient had no relevant history. She was first seen on October 12th when the blood-pressure and urine were normal.

The blood-pressure rose gradually but there were no other symptoms or signs of toxaemia, and she was treated as an out-patient until December 30th.

On admission the blood-pressure was 175/100, but there was no albuminuria.

The fundi showed marked narrowing of the arteries and transient spasm of a few branches.

Blood urea	24 mg. per 100 c.cm.
Blood cholesterol	110 mg. per 100 c.cm.
Blood uric acid	3.6 mg. per 100 c.cm.
CO_2 combining power	48.4 vols. per cent.

Urea concentration was good.

After a fortnight in hospital the blood-pressure had fallen to 140/90, and the spasm of the retinal

vessels was absent - even the attenuation was hardly noticeable. The patient went into labour spontaneously on January 21st and was normally delivered. The blood-pressure subsequently fell to 125/80 and remained low. She was seen again on March 15th and the fundi, blood-pressure and urine were all normal.

This case presents no remarkable features - the arterial constriction and spasm corresponded in time to the raised blood-pressure, and disappeared as it fell. As far as one can judge the toxaemic process ceased abruptly with the termination of the pregnancy, and left no residual lesion. Unfortunately this type of case was exceptional in the series examined, most patients presenting anomalous and puzzling features at some stage in their progress.

Case XIV. D.U. Aet.39. 2-gravida.

Due February 2nd. This patient had had one normal pregnancy two years previously, and had no noteworthy history. She was first seen in August, when the blood-pressure was 130/80 and the urine clear.

On September 7th the blood-pressure was 155/90 and there was marked albuminuria, so she was forthwith admitted. A fortnight later she was discharged at her own request with the urine normal but blood-pressure 145/85.

On November 16th she was re-admitted with blood-pressure 160/95 and albuminuria. At this time the

retinal arteries were normal but there was mild diffuse oedema of the retina and discs, and venous dilatation.

Blood urea	18 mg. per 100 c.cm.
Blood cholesterol	116 mg. per 100 c.cm.
Blood uric acid	3.2 mg. per 100 c.cm.
CO_2 combining power	41.4 vols. per cent.

Urea concentration was satisfactory.

There was no oedema or abnormal weight increase. After a few days rest in hospital the retinal oedema disappeared leaving a diffuse fine mottling of the fundi which was present till she went home against advice on December 21st, with blood-pressure still 160/90.

This patient did not attend the ante-natal clinic subsequently, but she went into labour on January 16th and delivered a live premature infant. She stated she had had no symptoms.

The fundi were examined the day after delivery and showed venous dilatation but no trace of oedema or mottling remained and the arteries were normal.

She was discharged with blood-pressure 130/90 and did not report for post-natal examination.

In this case no narrowing of the retinal arteries was noted at any time, but from experience this does not necessarily mean that it was never present, and still less does it mean that there was no vascular lesion in other tissues. The retinal oedema which appears to be associated with venous dilatation (Mylius[47]) was not

observed in a large proportion of cases in this series, but as it also appears to be transient, this fact is not particularly significant.

The fact that a fortnight after delivery, the blood-pressure in this case was higher than at any time during the pregnancy is peculiar and unusual, and only occurred in one other case - No.XII - a probable case of antecedent vascular disease. No conclusion, however, can be drawn in the absence of a follow-up period.

Case XV. I.K. Aet. 24. Primigravida.

Due February 15th. This patient was first seen in October and blood-pressure and urine were then normal.

On January 6th blood-pressure was 144/85 and did not fall with home treatment and rest. A week later she was admitted with blood-pressure 160/95 and moderate albuminuria.

At this time the fundi were normal.

Blood urea	21 mg. per 100 c.cm.
Blood cholesterol	122 mg. per 100 c.cm.
Blood uric acid	2.8 mg. per 100 c.cm.
CO_2 combining power	46 vols. per cent.

Urea concentration was good.

The blood-pressure fell to 140/85 in hospital and the albumin cleared from the urine. The fundi remained normal throughout.

On January 28th she was spontaneously delivered, and the blood-pressure immediately fell to normal and

remained low. The fundi showed no change.

This case seems to have been of a mild acute nature, and the vascular process apparently did not involve the retinal vessels, though this cannot be stated with certainty for the reasons mentioned before.

Case XVI. E.W. Aet.21. Primigravida.

Due March 19th. This patient was first seen on November 15th and her blood-pressure was 170/110. She was immediately admitted.

On admission there was no albuminuria but this made its appearance two days later.

The fundi were examined and showed diffuse mottling as in the previous case after the oedema had subsided. The veins were very full and there was heightening of the arterial reflex but no narrowing.

Blood urea 33 mg. per 100 c.cm.
Blood uric acid 4.3 mg. per 100 c.cm.

The blood-pressure remained high, about 170/100 but the albumin cleared from the urine, and on December 2nd the patient went home against advice. At this time the mottling of the fundi had disappeared, but otherwise the appearance had not changed.

She continued to attend the ante-natal clinic and on January 11th spasm and narrowing of the retinal arteries was noted, but inspite of a persistently raised blood-pressure she repeatedly refused re-admission. On January 25th the foetal heart was not heard, the blood-

pressure was 160/90 and apart from some heightening of the arterial reflex the fundi appeared normal.

On January 30th she was admitted in labour and a macerated foetus was expelled. After this the blood-pressure slowly fell to 135/90 at which level it remained. The patient did not report back subsequently as instructed. The fundi showed no abnormality on discharge.

In this case the fundus changes appeared to run a parallel course with the blood-pressure and general condition, until delivery; it will be noticed that the spasm and narrowing of the arteries together with venous dilatation all disappeared after the intrauterine death of the foetus, which is suggestive of an acute process abruptly ceasing at this point. The blood-pressure, however, did not fall abruptly then and did not fall to normal levels by the end of the puerperium - the significance of this lies in the patient's future medical history.

Case XVII. M.A. Aet.38. 4-gravida.

Due February 17th. This patient had had 'kidney trouble' with her last pregnancy but not severe enough to warrant admission to hospital.

She was first seen in October; at that time the blood-pressure was 115/70 and the urine normal.

From the middle of November the blood-pressure gradually rose, and on January 3rd she was admitted

complaining of giddiness and nausea. The blood-pressure was 155/90, there was no albuminuria and the retinal vessels were normal but there was some localized oedema of the retina in the macular region.

Blood urea	21 mg. per 100 c.cm.
Blood cholesterol	162 mg. per 100 c.cm.
Blood uric acid	3.8 mg. per 100 c.cm.
CO_2 combining power	50.2 vols. per cent.

Urea concentration was good.

By January 13th the blood-pressure had fallen to 135/85 and there were no symptoms. The retinal oedema had disappeared and the patient was discharged.

She was re-admitted four days later complaining of visual phenomena and headaches, but the blood-pressure was only 130/80 and the fundi were normal.

Blood chemistry was the same as previously except that cholesterol had fallen to 152 mg. per 100 c.cm.

The blood-pressure fluctuated from 130/80 to 150/90 but there was no albuminuria and no fundus change. The symptoms struck one as being psychologically engendered, and the patient was normally delivered on February 9th.

The puerperium was uneventful and she went home on February 20th with blood-pressure and fundi normal.

This case appears to have been a recurrence of a very mild condition, typical of that described by Stander as "Low Reserve Kidney", and of the cases to which Professor F.T.Browne and Miss Gladys Dodds(53)

refer to when they state that "pregnancy is the most delicate test of renal function". These latter workers claim to have reproduced the condition experimentally in rabbits which had chronic mild oxalate nephritis only discernible clinically during pregnancy. This seems to be insufficient evidence to exculpate all other tissues than the kidneys from the process, and the presence of retinal oedema even as mild and transient as in the present case rather suggests that the process is of a more vicarious nature.

Case XVIII. A.McC. Aet.25. Primigravida.

Due February 18th. This patient had had two miscarriages 2 years and 3 years previously, but no other relevant history. The blood-pressure on her first antenatal visit in August was 128/85 and the urine was clear. No signs of toxaemia were noticed until February 3rd when she was found to have a blood-pressure of 160/100 and marked albuminuria and was admitted to hospital.

The systolic blood-pressure came down with rest but the diastolic pressure remained high and albumin persisted in the urine.

On admission the fundi had a curious patchy appearance - strips of depigmentation especially in the lower parts suggesting the distribution of choroidal vessels. The retinal arteries were narrow.

Blood urea 27 mg. per 100 c.cm.
Blood cholesterol 108 mg. per 100 c.cm.

Blood uric acid 4.2 mg. per 100 c.cm.
CO_2 combining power 46 vols per cent.

Urea concentration was within normal limits.

On February 10th the membranes were ruptured and a live child was successfully delivered.

The blood-pressure fell to 120/80 but subsequently rose to 130/90 at which level it remained till the patient was discharged. The fundi remained unchanged and some white choroidal dots appeared below the macula on the right side.

Six weeks after delivery the blood-pressure and fundi were unchanged.

The fundi of this patient suggest some condition of longer standing than the present pregnancy could account for; it is possible that the two previous miscarriages which occurred at 3 months and 4 months may have been due to a toxaemic process occurring early in pregnancy, but conjectures of this nature while interesting, are of no practical value. It is interesting to note, however, that the blood-pressure was within normal limits when this patient was seen early in the present pregnancy, and apart from the picture the fundi presented, there was no indication of any vascular defect.

Case XIX. A.R. Aet.27. Primigravida.

This patient was a primigravida due on February 20th. When first seen in October, blood-pressure was 130/80 and urine normal.

The blood-pressure slowly rose and on January 13th she was admitted.

On admission, blood-pressure was 165/95 but there was no albuminuria, oedema or symptoms.

The fundi were examined and marked oedema of the discs and central areas of the retina were observed. The arteries were narrow but there was no definite spasm.

Blood urea	16 mg. per 100 c.cm.
Blood cholesterol	168 mg. per 100 c.cm.
Blood uric acid	3.2 mg. per 100 c.cm.
CO_2 combining power	41.2 vols. per cent.

Urea concentration was good and there was no abnormal weight increase.

Two days later the patient went home against advice with the blood-pressure and fundi unchanged.

When she was next seen, on January 22nd, the oedema had disappeared, but the veins were dilated and crushed where the arteries crossed. The arteries were still narrow. There was no history of any visual disturbance.

The patient was re-admitted at this time with blood-pressure 150/95 at which level it remained until labour was induced by medical induction on February 1st. No oedema of the discs had been noticed on subsequent examination of the fundi and no spasm, but the attenuation persisted.

After a normal delivery, the blood-pressure fell to 135/90 and did not alter while she remained in

hospital. The attenuation of the retinal arteries, however, disappeared.

The extremely transitory nature of the fundus lesions in pregnancy toxaemia is again emphasized in this case. Marked oedema may appear and disappear very rapidly - it happened to be observed in this case, and arterial spasm which was very probably present at some stage, was not observed.

Six weeks post-partum this patient's blood-pressure was normal.

Case XX. V.R. Aet.19. Primigravida.

Due February 24th. This patient had a blood-pressure of 140/85 when she first attended the ante-natal clinic on December 6th. A month later it was 145/90 and there was moderate albuminuria.

She was admitted to hospital on February 13th with the condition much the same after having shown slight improvement. At this time there was slight haziness of the disc margins but no apparent alteration in the vessels.

Blood urea	37 mg. per 100 c.cm.
Blood cholesterol	94 mg. per 100 c.cm.
Blood uric acid	3.4 mg. per 100 c.cm.
CO_2 combining power	48 vols. per cent.

Urea concentration was excellent.

With rest the albumin disappeared from the urine and the blood-pressure did not rise. Apart from the first examination, the fundi remained normal throughout.

A spontaneous delivery occurred on February 20th after which the blood-pressure fell to 120/90 and remained low.

This case was apparently of a very mild and tractable nature, the mild oedema noted on the first examination of the fundi disappeared as the clinical condition improved.

Case XXI. L.G. Aet.24. Primigravida.

Due February 26th. This patient was admitted to hospital in July as a case of hyperemesis gravidarum at 8 weeks. The case was not severe, and responded quickly to treatment. At that time blood-pressure and urine were normal.

In November the blood-pressure began gradually to rise but no other signs or symptoms of toxaemia occurred.

She was admitted on February 10th with blood-pressure 150/90. The fundi were normal.

Blood urea	22 mg. per 100 c.cm.
Blood cholesterol	146 mg. per 100 c.cm.
Blood uric acid	2.4 mg. per 100 c.cm.
CO_2 combining power	48 vols. per cent.

Urea concentration was good.

On February 16th this patient was normally and spontaneously delivered.

Post-partum, the blood-pressure fell to normal and remained low, and there was no change in the fundi.

There is no feature of any interest in this case, except the possible significance of the association of

late pregnancy toxaemia with hyperemesis in the early weeks.

Case XXII. H.M. Aet.28. Primigravida.

This patient was first seen in September when she was about fourteen weeks pregnant. The blood-pressure was then 142/85 but there was no history to suggest vascular or renal disease. It remained at about this level and there was no albuminuria till February 17th when she was admitted. At this time the blood-pressure was 150/110.

Blood urea	27 mg. per 100 c.cm.
Blood cholerterol	132 mg. per 100 c.cm.
Blood uric acid	2.1 mg. per 100 c.cm.
CO_2 combining power	49.8 vols. per cent.

Urea concentration was good, and there was no oedema or excessive increase in weight. The retinal arteries were narrow and there was diffuse fine mottling of the fundus background similar to that seen in other cases with subsiding oedema. Spasm of one branch of the right retinal artery was observed.

The fundus picture did not alter, and the patient spontaneously delivered herself on February 23rd. The blood-pressure subsequently subsided and remained low, but the attenuation of the retinal arteries persisted and definite oedema of the nasal side of the right disc appeared.

In this case again the discrepancy between blood pressure readings and the state of the fundi is apparent. It is possible that the subsidence or persistence of fundus lesions in the puerperium has more prognostic significance than the blood pressure readings, but this is pure speculation.

Case XXIII. R.N. Aet.29. Primigravida.

Due March 8th. This patient was seen when she was sixteen weeks pregnant. Blood-pressure and urine were then normal, and it was not until January that hypertension was recorded. This increased and on February 14th the blood-pressure was 170/95, but she refused admission. There was no albuminuria and the fundi were normal at this time.

Blood urea	22 mg. per 100 c.cm.
Blood cholesterol	156 mg. per 100 c.cm.
Blood Uric acid	3.4 mg. per 100 c.cm.
CO_2 combining power	46.4 vols. per cent.

On February 17th a healthy infant was spontaneously delivered, and the blood-pressure subsequently fell and remained normal. The fundi were normal throughout.

Case XXIV. W.F. Aet.22.

Due March 19th. This case was very similar to the last one. She was first seen on December 28th with a normal blood-pressure and urine. On January 25th the blood-pressure was 150/85, but the fundi were normal.

No albuminuria or symptoms occurred and though the hypertension persisted, the fundi remained normal.

The patient was delivered spontaneously on January 24th and the blood-pressure fell to 130/90 but not below this figure. The fundi remained normal.

Blood analysis was not done in this case.

The retinal arteries were narrow and there was diffuse fine mottling of the fundus background similar to that seen in other cases with subsiding oedema. Spasm of one branch of the right retinal artery was observed.

The fundus picture did not alter, and the patient spontaneously delivered herself on February 23rd. The blood-pressure subsequently subsided and remained low, but the attenuation of the retinal arteries persisted and definite oedema of the nasal side of the right disc appeared.

In this case again the discrepancy between blood-

pressure readings and the state of the fundi is apparent. It is possible that the subsidence or persistence of fundus lesions in the puerperium has more prognostic significance than the blood-pressure readings, but this is pure speculation.

Case XXV. C.C. Aet.28. 2-gravida.

This patient's previous pregnancy 8 years ago had been uncomplicated, and she had no medical history.

She was first seen in November, 24 weeks pregnant. The blood-pressure of 140/75 was discounted to a certain extent by the extreme nervousness of the patient. It was invariably elevated when she came to the ante-natal clinic, but the diastolic pressure was usually low. On December 20th, however, it was recorded as 150/90 and she was admitted. The fundi were normal.

Blood urea	18 mg. per 100 c.cm.
Blood cholesterol	170 mg. per 100 c.cm.
Blood uric acid	2.4 mg. per 100 c.cm.
CO_2 combining power	46 vols. per cent.

She was discharged with blood-pressure 150/75 on January 23rd and fundi still normal.

No change occurred in the condition till March 3rd when she was re-admitted with albuminuria and blood-pressure 160/90.

The blood chemistry had not altered significantly, there was no oedema or other symptoms and urea concen-

tration was good. The retinal vessels were noticed for the first time to be narrow.

On March 11th a spontaneous delivery occurred, the clinical condition having improved while in hospital. The narrowing of the retinal vessels subsequently disappeared though the blood-pressure readings remained about 145/70.

One was inclined to accredit the persistent hypertension to the extremely nervous type of patient here - she was suggestive of a hyperthyroid state, and in view of the low diastolic pressure, it is unlikely that any organic lesion was present. The diastolic pressure only rose towards the end of the pregnancy when the attenuation of the retinal arteries was noted. The significance of this observation is only estimable after months or years of following up.

Case XXVI. E.C. Aet. 23. Primigravida.

Due February 29th. This patient was first seen in September. She had no relevant history and her blood-pressure was normal. In January it started to rise and on February 3rd she was admitted.

On admission blood-pressure 155/80, the urine was clear, and the retinal vessels showed heightened arterial reflex but no attenuation.

Blood urea	26 mg. per 100 c.cm.
Blood cholesterol	98 mg. per 100 c.cm.
Blood uric acid	4.66 mg. per 100 c.cm.
CO_2 combining power	41.2 vols. per cent.

Urea concentration was good. There was no albuminuria, oedema or abnormal weight increase.

The blood-pressure rose to 160/95 and albumin appeared in the urine. By February 28th there was definite narrowing of the retinal arteries but no spasm was observed.

Labour was induced by bougies on March 12th after medical induction had failed, and a live child was delivered. Several large placental infarcts were present.

The blood-pressure did not subsequently subside and was still 145/80 at the end of the puerperium. The narrowing of the retinal arteries also persisted.

It is possible that this patient's future health may have been adversely influenced by the failure to induce labour earlier. The blood-pressure was persistently raised above 150 systolic for five weeks before delivery, ans this time might well have been reduced.

The placental infarcts in this case were very striking - more than half the placental tissue was replaced by them. The possibility of their bearing on the cause of pregnancy toxaemia has already been mentioned in discussing the aetiology of the condition.

Case XXVII. M.M. Primigravida. Aet. 26.

Due March 7th. This patient was first seen in December, her past history revealed nothing of any note,

and urine and blood-pressure were normal.

On February 24th the blood-pressure was found to be 164/100 and there was moderate albuminuria. Immediate admission was advised.

On admission blood-pressure was 145/90, and there was albumin in the urine.

The retinal vessels showed heightened arterial reflex but no other change.

Blood urea	21 mg. per 100 c.cm.
Blood cholesterol	160 mg. per 100 c.cm.
Blood uric acid	3.3 mg. per 100 c.cm.
CO_2 combining power	49.5 vols. per cent.

Urea concentration was normal and there was no oedema.

Labour was indiced on March 1st without change in blood-pressure or fundi.

After an initial fall to 120/80, the blood-pressure rose again, and was 140/80 at the end of the puerperium. The heightened arterial reflex was still present in the retinal vessels.

Case XXVIII. V.D. Primigravida.

Due March 26th. This patient was seen in December when the blood-pressure and urine were normal.

On February 24th the blood-pressure was 118/75 but the following week it had risen to 150/110 and there was very marked albuminuria.

On admission at this time the fundi showed no abnormality.

Blood urea	19 mg. per 100 c.cm.
Blood cholesterol	119 mg. per 100 c.cm.
Blood uric acid	2.2. mg. per 100 c.cm.
CO_2 combining power	53.8 vols. per cent.

Urea concentration was good.

With treatment the blood-pressure subsided to normal and the albuminuria cleared. The fundi remained normal.

The blood-pressure remained low, and no abnormal phenomena occurred. A normal delivery terminated the pregnancy on March 27th, and the puerperium was uneventful.

This appears to have been an example of acute toxaemia which subsided completely during the pregnancy. It is possible that some of the transient phenomena observed in other cases such as oedema and spasm may have been missed here, but in view of the progress of the case they would have had little significance as regards ultimate prognosis, even if they were observed.

Case XXIX. S.W. Aet.30. 3-gravida.

Due March 25th. This patient had had two previous uncomplicated pregnancies. When seen first in December the blood-pressure was 135/85 and the urine was clear.

On January 31st this patient came to the ante-natal clinic complaining of headache, oedema of the hands, face and legs; there was marked albuminuria and the blood-pressure was 190/120. The weight was 15st. 7 lbs.

She was immediately admitted. The fundi appeared perfectly normal.

Blood urea	18 mg. per 100 c.cm.
Blood cholesterol	100 mg. per 100 c.cm.
Blood uric acid	3.2 mg. per 100 c.cm.
CO_2 combining power	47.3 vols. per cent.

Urea concentration was satisfactory.

The condition improved with conservative treatment. She lost 7 lbs in a week and the albumin cleared from the urine. The blood-pressure remained at about 145/90 and on February 23rd the retinal arteries appeared narrow for the first time. After this traces of albumin were found in the urine at intervals, and on March 8th spasm of some branches of the retinal arteries was observed, and persisted till delivery.

The blood-pressure did not vary much, and spontaneous delivery occurred on March 17th. After delivery the blood-pressure subsided and no further spasm of the retinal arteries was seen. At the end of the puerperium she was discharged with blood-pressure at its original level of 135/85. No subsequent observations were made.

This patient, admitted to hospital with the whole gamut of pre-eclamptic symptoms and signs, at that time showed no fundus lesion, but afterwards when the clinical condition was evidently improving, narrowing and spasm of retinal arteries was observed, so that in this case again the ophthalmoscope gave very little help in dealing with the clinical condition. Possibly if

a number of similar cases were followed up for a sufficiently lengthy period, some prognostic significance in the ophthalmoscopic picture might be deduced.

Case XXX. A.B. Aet.31. Primigravida.

Due April 1st. This patient had a blood-pressure of 160/90 and mild albuminuria when she first visited the ante-natal clinic in January, and the fundi showed heightened arterial reflex. No relevant past history was elicited.

On admission on January 30th the blood-pressure was 150/85, but the urine was free of albumin.

Blood urea	23 mg. per 100 c.cm.
Blood cholesterol	128 mg. per 100 c.cm.
Blood uric acid	4.2 mg. per 100 c.cm.
CO_2 combining power	42.9 vols. per cent.

Urea concentration was satisfactory.

The right fundus showed no abnormality, but the left one showed, in addition to heightening of the arterial reflex, spasm of some smaller arteries and a few white dots.

A week later, these dots had disappeared and spasm of the arteries was not seen though the blood-pressure had risen to 170/90. Spasm was again seen subsequently on several occasions.

Labour was induced by medical induction and she was normally delivered on March 18th. The blood-pressure on the day following delivery was 190/90. It subsided somewhat in the puerperium, but was still 140/85 on

discharge.

This patient again illustrates the transitory nature of the spasm observed in these cases, and the lack of any correlation between presence of this phenomena and the height of the blood-pressure at any particular time.

The white dots in this case, similar to those seen in cases XI and XII, were thought to be possibly cholesterol deposits, but they were not associated with a high blood-cholesterol in any of the three cases.

Six other cases were studied and examined ophthalmoscopically, but they are not reported as in one way or another they were all incomplete, and no feature of particular interest was observed in any of them. Similar phenomena to those already frequently described occurred, and no useful purpose can be served by multiplying these data.

It is worthy of note here that visual symptoms did not occur frequently in the cases under observation - when they did, however, they appeared not to be correlated in any way with any fundus lesions. They were vague, and transitory when they occurred, and similar in type to the vague symptoms complained of by many pregnant women in various parts of the body. It would be impossible to take all these complaints seriously. At the same time, in the rarer cases where exudate and haemorrhage occurs, visual defect may very likely be marked and of serious import. This type of

case, however, will practically invariably be of obvious clinical severity, and the fundus lesion will be gross and easily recognizable.

In the average type of case such as most of the present series were, careful enquiry has failed to elicit temporary visual defect such as might have occurred if severe, widespread spasm of the retinal arteries had occurred.

TABLE I. Clinical Features

Case	B.P. normal when first seen	B.P. normal at end of puerperium	B.P. normal 6 weeks after delivery	Albuminuria	Fundi normal throughout
I	-	+	?	-	+
II	-	-	?	+++	+
III	+	+	+	+++	-
IV	+	-	-	+	-
V	-	-	?	++	+
VI	+	-	?	++	-
VII	-	-	?	-	-
VIII	+	+	+	++	-
IX	+	-	?	-	-
X	-	-	+	+	-
XI	+	-	-	+	-
XII	- Probably - essential - hypertension			+	-
XIII	+	+	-	-	-
XIV	-	-	?	+	-
XV	-	+	?	+	+
XVI	-	-	?	+	-
XVII	+	-	?	-	-
XVIII	+	-	-	++	-
XIX	-	-	+	-	-
XX	-	+	?	+	-
XXI	+	+	?	-	+
XXII	-	+	?	-	-
XXIII	+	+	?	-	+
XXIV	+	-	?	-	+
XXV	-	-	?	++	-
XXVI	+	-	?	+	-
XXVII	+	+	?	+	-
XXVIII	+	-	?	+++	+
XXIX	-	-	?	+++	-
XXX	-	-	?	-	-

Urea concentration was normal in every case; blood urea and blood cholesterol were within normal limits without exception.

Table II. Eyeground Changes

Case	Eye-ground change occurred	Atten-uation of arteries	Spasm of arteries	Oedema of disc or retina	Fundus normal after delivery
I	–	–	–	–	+
II	–	–	–	–	+
III	+	+	–	–	+
IV	+	+	–	+	–
V	–	–	–	–	+
VI	+	+	–	–	+
VII	+	–	–	–	+
VIII	+	+	+	–	+
IX	+	+	–	+	–
X	+	+	+	–	+
XI	+	+	+	–	–
XII	+	–	–	+	–
	Probably essential hypertension				
XIII	+	+	+	–	+
XIV	+	–	–	+	+
XV	–	–	–	–	+
XVI	+	+	+	+	+
XVII	+	–	–	+	+
XVIII	+	+	–	–	–
XIX	+	+	–	+	+
XX	+	–	–	+	+
XXI	–	–	–	–	+
XXII	+	+	+	+	–
XXIII	–	–	–	–	+
XXIV	–	–	–	–	+
XXV	+	+	–	–	+
XXVI	+	+	–	–	–
XXVII	+	–	–	–	–
	Heightened reflex only				
XXVIII	–	–	–	–	+
XXIX	+	+	+	–	+
XXX	+	+	+	–	+

DISCUSSION OF RESULTS

The results of this investigation have, on the whole, been disappointing. Very little help has been obtained from ophthalmoscopic examination of patients with hypertensive toxaemia of pregnancy, as regards their immediate prognosis and the general conduct of the case. Certain fundus lesions have been repeatedly observed, however, and these have certain notable characteristics: it is possible that if the cases could have been followed up for two or three years after the toxaemic pregnancy, some correlation between the original ophthalmoscopic findings and the future health of the patient could have been established. Certainly from the immediate point of view, the results have appeared frequently anomalous and sometimes even misleading.

Of the thirty cases described, eight showed no fundus abnormality at any time. These eight showed no features in common - some were severe, and some were clinically mild, and the actual height of the blood pressure varied considerably. The average biochemical values for the seven patients with normal fundi in whom estimations were made were:

Blood urea	21.3 mg. per 100 c.cm.
Blood cholesterol	126.0 mg. per 100 c.cm.
Blood uric acid	3.0 mg. per 100 c.cm.
CO_2 combining power	47.4 vols per cent.

The average values for the whole series (27 cases) were:

Blood urea	21.7 mg. per 100 c.cm.
Blood cholesterol	127.0 mg. per 100 c.cm.
Blood uric acid	3.18 mg. per 100 c.cm.
CO_2 combining power	45 vols. per cent.

For cases which showed some fundus lesion at some stage the average values were:

Blood urea	23 mg. per 100 c.cm.
Blood cholesterol	129 mg. per 100 c.cm.
Blood uric acid	3.3 mg. per 100 c.cm.
CO_2 combining power	44 vols. per cent.

The slight increase in uric acid values and the diminution in the alkali reserve which is apparent in the whole group, is exaggerated in the cases which had fundus lesions, whereas the group with normal fundi had values within normal limits. This may be significant, but the only conclusion which can reasonably be drawn from these facts is that on the whole the cases showing fundus lesions were more severe than those with normal fundi, though this is hardly noticeable when considering the individual cases. The values given in reporting the cases were those taken at the height of the disease - in many cases repeated estimations were made, but these were omitted for the sake of brevity as no significant alterations were observed, except that as the clinical condition improved, the alkali reserve

increased.

The most striking feature of the fundus lesions themselves was their extremely transitory nature, especially the spasm and oedema which are the two phenomena most emphasized in the literature (Mylius, Wagener, and others). General attenuation of the arteries and heightening of their reflex did not come and go so rapidly - when they appeared they usually persisted until the termination of pregnancy though not invariably. These latter, however, are less characteristic of an acute state, and therefore were thought initially to be less suitable phenomena on which to concentrate. Now it has become apparent that it is impossible to detect early potentially severe and eclamptic patients by means of the ophthalmoscope, and that, apart from the indication of acute diffuse retinitis to terminate pregnancy, the value of the ophthalmoscopic examination of toxaemic patients is practically confined to the question of remote prognosis. The remote prognosis, however, is extremely important in these cases, as it seems very probable that the lives of a considerable number of women are shortened by many years as a direct result of toxaemic pregnancy. This question will be discussed later, but at the risk of being criticized for repetition, it must again be emphasized that, as regards remote prognosis, no period of observation under a year can

be of any practical value from the point of view of estimating the frequency of chronic vascular disease as a sequel to pregnancy toxaemia.

Authorities such as Masters[51] and Gibson[49] in their publications imply a definite correlation between the fundus picture and the course of a toxaemic pregnancy which was not found in the present investigation. Masters, examining 33 cases with systolic blood pressure exceeding 150 mm.Hg. found attenuation of the retinal arteries in every one; cases of "Low Reserve Kidney" were excluded - a condition defined as "moderate rise in blood pressure with mild albuminuria which disappears by the end of the pureperium." As one cannot tell during pregnancy whether hypertension will subside by the end of the puerperium, this appears to be a doubtful entity, and in any case one cannot wait till the puerperium to diagnose a potential eclamptic, so that the definition is of no practical value.

Hallum[54] in 1936 found attenuation and sometimes spasm and oedema in 84.5% cases with blood pressure over 150/100. He came to the conclusion that the absence of albuminuria has no significance in relation to eyeground changes and that excessive gain in weight is not necessarily associated with toxaemia, two statements confirmed by the present series of cases. He and Wagener both consider that organic vascular changes supervene after about an average of ten days' function-

al angiospasm - this was not confirmed. Attenuation and sometimes spasm of retinal arteries was known to exist in some of the cases described above, for more than ten days, and no evidence of sclerosis was present. Diffuse retinitis is considered by both these authorities to indicate impending organic lesions and therefore termination of pregnancy is advised. Such retinitis should be capable of distinction from the retinitis of chronic vascular or renal disease where the organic lesions are reaily recognizable. Schiotz[55] found that 27 of 33 cases which had diffuse retinitis subsequently exhibited signs of chronic vascular disease.

Gibson[49] emphasizes that if sclerosis occurs, as is shown probably by narrowing of the lumen of the retinal arteries and crushing of the veins, then the process is irreversible and progressive. A latent period will probably occur, he says, lasting 4 to 12 years during which time the blood pressure may be normal, and then the terminal stage will begin with symptoms according to whatever system is chiefly affected by the vascular disease. Retinal arteriosclerosis will progress to hypertensive retinopathy with possibly old pigment scars to represent the initial toxaemia. Of 39 cases, Gibson reported 5 with normal fundi, 23 in the pre-organic phase and 11 with organic changes. He found that at times clinical improvement was belied by the ophthalmoscope,

and found in these cases he was able to forecast a sudden rise in blood pressure.

Fan[50] examined 110 Chinese patients, and found that residual hypertension six weeks postpartum was commoner in cases with fundus lesions than in those without them, but as 30% of the latter had residual hypertension, the presence or absence of fundus lesions would not seem sufficient grounds for issuing a prognosis; in any case six weeks postpartum readings of blood pressure do not indicate whether or not there is permanent vascular damage.

Miss Jones[46] found that after intervals varying from 5 months to 2 years after a toxaemic pregnancy, the proportion of residual vascular and renal disease increased directly with the degree of the original fundus lesion. Other points of interest in her paper are that she found no fundus lesions in any case whose systolic blood pressure was below 150 mm. Hg. and that an average of 13 days' toxaemia was associated with a normal retina. From the limited number of cases examined, one is unable to confirm these latter statements, but Miss Jones did not pay much attention to the vessels, and reported only diffuse changes of the retina and disc.

In conclusion, the evidence seems to support the opinion of Wagener,[48] Schiotz,[55] Mylius,[47] and others that the primary retinal lesion in pregnancy

toxaemia, when any lesion occurs, is vasoconstriction frequently associated with spasm, and that all other lesions such as oedema, haemorrhage, and exudate are secondary to that constriction and the resultant capillary stasis. The initial spasm, however, is not necessarily visible at any particular time, being frequently transient, so that the other lesions may be observed in its absence. It is impossible to say that spasm is absent in any particular case, but in view of the number of patients with normal fundi on repeated examination, it seems probable that in these cases the retinal vessels are unaffected or unresponsive. If this is so then the retinal circulation is not necessarily an accurate index of the general circulation.

It may be said here that the detection of arterial spasm requires considerable time, patience, and practice which advantages are usually denied the average practitioner in charge of antenatal clinics. By the time gross lesions have occurred in the retina, the case has probably been recognized as a severe one by other means than the ophthalmoscope, so that the place of this instrument in routine antenatal work is very doubtful, especially in view of the anomalous results obtained by its use.

It is possible that with a more elaborate technique more coherent results would have been obtained - for instance incipient spasm might be provoked by vaso-

pressin injections (this has already been tried as a diagnostic test for toxaemia by Schockaert and Lambillon[27] and by de Valera and Kellar,[29] but the fundi were not observed) or by means of the ophthalmodynamometer an accurate reading of the pressure within the retinal arteries could be estimated, but these procedures would belong more to the realm of research than to ordinary practice.

REMOTE PROGNOSIS OF PREGNANCY TOXAEMIA

The fact that certain cases of hypertensive toxaemia of pregnancy become cases of chronic vascular disease is undoubted. Whether such patients have a tendency to hypertension which is dramatized by pregnancy, but would eventually develop hypertension apart from the pregnancy, or whether the pregnancy actively initiates the process, is a matter for conjecture. Certainly when chronic vascular disease dates from a toxaemic pregnancy, the post mortem picture is frequently identical with that of a case dying from vascular disease when pregnancy has never occurred. It is possible that the fact that essential hypertension is commoner in women than in men (65% cases occur in women according to Blackford[56]) may be due to the occurrence of hypertension in pregnancy.

An attempt to differentiate between renal and vascular disease in this connection seems to be futile - the vascular structure of the kidney may be affected more than the vessels of other organs, in which case signs of impaired renal function will predominate. Volhard[33] stated that the typical renal lesion in acute toxaemia is ischaemia of the glomerulus consequent upon spasm of the afferent arteriole. If the patient dies in the acute stage, however, tubular degeneration may be marked whereas in a patient who survives the pregnancy

and later dies of uraemia, there is usually tubular atrophy. The condition known as "malignant nephrosclerosis" appears to be abalogous to the vascular sclerosis following many toxaemic pregnancies - the condition is not confined to the kidney but consists of widespread proliferative endarteritis and degeneration of the renal tubules. The renal changes in this condition are characteristically focal rather than diffuse. McKelvey and McMahon(31) describe post mortems on 13 cases of previous pregnancy toxaemia - seven of these showed typical nephrosclerosis and died 2 to 7 years after the initial lesion; the other five showed "acute tubular nephrosis." One had simple renal arteriosclerosis.

Herrick and Tillman(32) did 11 similar post mortems and found vascular sclerosis the predominating pathological feature in 7 of them.

As regards the frequency with which chronic vascular disease followes pregnancy toxaemia, the authorities vary, but most figures indicate a strikingly high sequence. In 1927 Corwin and Herrick(57) reported that of 175 cases 40% had hypertension 6 months to 6 years after the pregnancy. It seems that the clinical severity of the toxaemia has no hearing on the occurrence of subsequent hypertension, but more its duration and the height of the ante-partum blood-pressure.

Peckham(39) and Mussey and Keith(38) were struck by the frequency with which "chronic nephritis" followed toxaemix pregnancies - the former found that

of 42 cases, only 5 did not show evidence of nephritis. If one includes vascular disease of the kidneys in "nephritis", this does not imply a contradiction to the results of other workers such as Teel and Reid[60] and Eastman,[58] who emphasized that the essential lesion is vascular, not renal, and showed that in many cases dying of uraemia, renal function frequently was normal until the terminal stages. Eastman took repeated photographs of the fundi of such patients and attached them to the case records to serve as a guide to the progress of the vascular disease. This is not only impracticable in most cases, but according to the results of the present investigation would not necessarily be a very accurate guide.

Herrick and Tillman[32] found that 50% of 594 cases of pregnancy toxaemia had subsequent hypertension, and Douglas[59] dealing with cases of "Low Reserve Kidney" found that 28% had subsequent hypertension and so concluded that the original diagnosis was wrong! This illustrates the futility of labelling these cases in the present inadequate state of knowledge concerning them - this term "Low Reserve Kidney" means nothing at all, and it is most unlikely that the type of case to which it is meant to refer has its primary lesion in the kidney. Mild cases cannot be distinguished from potentially severe ones in their early stages, and as the remote results of mild

and severe cases appear to be similar, they should all be treated equally seriously.

The effect of pregnancy on cases of antecedent vascular disease does not come within the scope of this paper, and will not be discussed, except to mention that it is to exacerbate the condition, subsequently making it difficult to define the primary lesion, and emphasizing their probable aetiological relationship.

The "Cold Test" of Hines and Brown[61] which is supposed to be positive in 98% of cases of essential and malignant hypertension (the latter is identical with "malignant nephrosclerosis" as described above) is said to indicate also latent hypertension in apparently normal cases, and has lately been tried in pregnancy toxaemia by Teel and Reid.[60] Briefly, the test consists of estimating the blood pressure response to the immersion of the hand in water and ice. The upper limit of normality is taken as 20 mm. Hg systolic rise. The results obtained in toxaemic cases were disappointing - only 11 out of 17 showed an exaggerated response. This is not really surprising as Pickering and Kissin[62] had already reported that the test was of little value in non-pregnant cases of essential hypertension.

The nature of the agent causing vaso-constriction in essential hypertension is still obscure, and whether such an agent is similar to the one active in

pregnancy toxaemia is unknown. Recently, however, some very interesting work on essential hypertension has been reported. Pickering,[41] abolishing vaso-motor tone in the forearm by warmth discovered that the blood flow through the forearm in essential hypertension was not increased, and therefore, assuming the capillary pressure to be normal (Ellis and Weiss[63]), the vaso-constriction must be due to some chemical agent and not to stimulation of vaso-motor nerves. In acute nephritis, by the same means, the blood-flow was found to be increased, indicating that a different mechanism must be at work. If, however, a chemical agent is the cause of vaso-constriction in essential hypertension and in the allied condition of pregnancy toxaemia, then such agent or agents must be fixed in some way as they are not circulating; transfusion of eclamptic blood does not cause hypertension or toxaamia in the recipient (Crispoliti[64]), nor does transfusion of blood from a hypertensive donor cause hypertension in the recipient. Also, repeated efforts to find a pressor substance in eclamptic blood have failed, proving that no substance capable of inducing vaso-constriction is circulating in sufficient quantities to do so. (A similar conclusion was reached in discussing the possibility of posterior pituitary as the constricting agent: cf. section on Aetiology).

Very recently Byrom and Wilson[42] reported some important experimental work on rats. They showed that

partial occlusion of one renal artery was frequently followed by the onset of hypertension which might be gradual or sudden, and that the other kidney and other organs often showed focal vascular lesions typical of malignant hypertension and nephrosclerosis, from which the clamped kidney was exempt. The significance of this work is not clear, but it confirms the assumption that no circulating toxin is necessary to explain these hypertensive states, and that increased intra-arterial tension in itself is of paramount importance in their aetiology. The duration of such tension is probably the vital factor in the production of organic vascular disease both in essential hypertension and in pregnancy toxaemia, but in the latter condition this is of great practical importance in view of the possibility of its control by termination of pregnancy.

Finally it seems reasonable to conclude that the condition known as hypertensive toxaemia of pregnancy may in the words of Peters(65) be "not an entity peculiar to pregnancy, but a manifestation of vascular disease dramatized by pregnancy." Any histological specificity of eclamptic lesions, he suggests, are an indication of the reaction of pregnant women to cardiovascular 'insults.' This seems a very credible hypothesis, and it is possible that when the aetiology of essential hypertension is clarified, pregnancy toxaemia will cease to be "a disease of theories" (Zweifel(66)).

SUMMARY AND CONCLUSIONS

After examining the evidence for and against the various theories regarding the aetiology of hypertensive toxaemia of late pregnancy, it is concluded that the disease is primarily a vascular one. Functional vaso-constriction of the smaller arteries is probably the initial lesion and this may be generalized or localized. If it is generalized certain organs may be predominantly affected to the comparative exclusion of others. Bio-chemical modifications, and alterations of metalbolism and vital ratios are probably due to the effect of this vaso-constriction on the liver and gastro-intestinal tract, possibly aggravated by such factors as high intra-abdominal pressure, or relative vitamin defici-ency (particularly B, which is apparently the only vitamin the organism is incapable of storing).

If functional vaso-constriction persists, sooner or later organic vascular change will supervene, and once this occurs the process is progressive and irre-versible. The exact stage at which organic changes in the vessels occur is impossible to recognize, but it is unlikely to occur in toxaemia of less than a fort-night's standing, irrespective of the clinical severity of the case. Once organic disease has started, the subsequent progress is very similar to the pathological processes which develop in essential hypertension and

nephrosclerosis, the degree of damage in the different organs varying with the individual case.

The nature of the pressor agent responsible for the initial functional vaso-constriction is unknown. Products of incomplete protein metabolism and over-active or unbalanced endocrines are favourite suspects, but neither are entirely satisfactory. A more tenable hypothesis is that the vaso-constriction is an allergic response to certain circumstances rather than a specific response to some abnormal or excessive substance.

The results of ophthalmological examination of 30 toxaemic patients are disappointing: the lesions observed were incapable of correlation with the blood pressure, the general clinical state, or blood chemistry. Further, except in extreme cases, the lesions were not gross and would be difficult for the average practitioner to appreciate, who has neither time not inclination to spend many hours examining fundi.

The conclusion was reached that the retinal vessels are not invariably an accurate index to the state of the rest of the vascular system, in which case the condition of these vessels would not appear to be an adequate observation on which to base any prognosis immediate or remote. Exceptions to this statement, however, are appreciated: in a case which develops diffuse retinitis, it may be taken that organic vascular disease is impending if it is not already established, and

therefore pregnancy should be terminated without delay. If sclerotic changes are observed in the retinal vessels which were not present before the pregnancy, or in its early stages, it is reasonable to assume that chronic vascular disease is developing, and that future prognosis should be guarded; a normal fundus, however, does not imply that the vascular system is healthy. Unfortunately the cases examined were not followed up for a sufficiently lengthy period to justify any observations with regard to their remote prognosis, but it may be worth while remarking that of the cases seen six weeks post-partum, all those with residual hypertension had had ante-partum fundus lesions.

Other results obtained exhibited no striking features; blood urea and cholesterol values are usually low in hypertensive toxaemia, uric acid is increased, and the alkali reserve is slightly diminished. Most cases showed no abnormal weight increase except with gross oedema, but even so it is probably beneficial to exclude salt from the diet as far as possible. In view of the demands of the foetus and a hypothetical deficiency of absorption, it seems inadvisable to reduce protein intake drastically.

Treatment of toxaemia of pregnancy on an endocrine basis is still in the experimental stage, and therapy recommended varies so much that it is a subject about which no conclusions are yet justified.

An alarming proportion of cases with pregnancy toxaemia appear to become cases of chronic vascular disease, and whether the pregnancy lights up a latent tendency to the disease or whether it actively initiates it, one is struck by the relationship between the two conditions. Variations in their histological lesions can be adequately explained by the acuteness of the former and the comparative chronicity of the latter. It is a reasonable hypothesis that the apparently unique characteristics of toxaemia and eclampsia occur in virtue of the pregnant state - these characteristics vary in the individual and a certain group may predominate, but no satisfactory basis for any subdivision of hypertensive toxaemia is accepted. It is less confusing to regard all such cases as manifestations of a similar pathological process, provided antecedent vascular and renal disease can reasonably be excluded. A common, or at any rate a closely allied cause for essential hypertension and hypertensive pregnancy toxaemia is suspected.

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